

**Identification and management of atypical Hemolytic Uremic Syndrome immediately post heart transplantation.**

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Abstract:

Atypical Hemolytic Uremic Syndrome (aHUS) is a serious hematologic disorder with high mortality if left untreated. A comprehensive literature review revealed only two cases of aHUS post heart transplantation. In both cases the disease developed after induction of calcineurin inhibitor therapy. We report a case of immediate post heart transplantation aHUS, manifested before the induction of, and therefore not associated with, calcineurin inhibitors.

## Patient Profile

IRB permission was obtained to report this interesting clinical case.

A 70-year-old female with familial end stage cardiomyopathy underwent a Heart Mate II (Thoratec, Pleasanton, Ca) Left Ventricular Assist Device (LVAD) placement and a year later she underwent orthotopic heart transplantation and LVAD explantation. Prior to surgery, the laboratory evaluation revealed the following: platelet count 139,000/cu mm, hemoglobin 9.2 gm/dl and creatinine 0.5 mg/dl. She received preoperatively mycophenolate mofetil and in the operating room a dose of steroids. The first postoperative day the platelet count was 135,000/cu mm and creatinine 1.1mg/dl. The second postoperative day severe thrombocytopenia was noted (22,000/cu mm) and the creatinine was 2.0 gm/dl with associated hyperkalemia (6.2 mmol/l). By the third postoperative day the platelet count did not improve (although platelet transfusion was administered for mediastinal bleeding) and she became anuric, with a creatinine level of 3.1 mg/dl and anemic (nadir hemoglobin level of 6.3 mg/dl). Further studies revealed an LDH of 1,460 U/l, haptoglobin level of less than 6 mg/dl and numerous schistocytes on the peripheral smear, consistent with microangiopathic hemolytic anemia (graph 1). Shiga toxin/EHEC test was negative and the patient did not have gastrointestinal related symptoms. After ruling out drug-induced thrombocytopenia (no antibodies against platelet factor 4, confirmed by serotonin release assay), disseminated intravascular coagulation, or other confounding possible causes, atypical HUS was ~~highly~~ suspected and plasma exchange therapy was initiated, in addition to continuous venous-venous hemofiltration. Thrombotic Thrombocytopenic Purpura (TTP) was excluded by a mildly reduced (>5%) ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity. At that point, mycophenolate and steroids were given as per our post heart transplant protocol, however; tacrolimus was held until post-operative day eight due to severely impaired renal function. An endomyocardial biopsy was performed on postoperative day thirteen and demonstrated grade 3R rejection. There was no evidence for humoral rejection. Since the patient started to show signs of recovery, she was treated with four doses of thymoglobulin. A repeat endomyocardial biopsy

on postoperative day twenty one demonstrated grade 0R rejection with Quilty effect. There was strong consideration to administer eculizumab therapy as a definitive treatment of complement mediated HUS, but in the setting of clinical improvement with plasma exchange this was never initiated. The patient was able to extubate on the eighth postoperative day. The patient received a total of twenty plasma exchange therapies and she was discharged in good clinical condition, with complete recovery of her renal function and normal hematologic values, after thirty three days of hospitalization.

## Discussion

Hemolytic Uremic Syndrome (HUS) is characterized by hemolytic anemia, thrombocytopenia, and renal failure caused by platelet thrombi in the microcirculation of the kidney and other organs. Typical HUS is triggered by infectious agents such as strains of E.Coli that produce powerful Shiga-like exotoxins, whereas atypical HUS can be genetic or acquired, and related to Shiga-like exotoxin. Atypical HUS has a poor prognosis, with death rates as high as 25% and progression to end-stage renal disease in many of these patients [3]. The association between HUS and calcineurin inhibitors therapy post solid organ transplantation including heart transplantation has been reported previously in literature [1, 2]. Interestingly, in our case the syndrome was manifested before initiation of tacrolimus therapy. The main triggering mechanism seems to be related to endothelial dysfunction.

Research has linked aHUS to uncontrolled activation of the complement system [3]. Several factors that contribute to complement regulation are expressed on or bound to endothelium. Triggers, such as infections or a profound inflammatory state, seen during cardiopulmonary bypass [4], are associated with complement activation. In the presence of events that enhance alternative pathway activation, in genetically susceptible individuals, this may lead to an uncontrolled mechanism, initiating the formation of the membrane-attack complex and leading to complement-mediated endothelial injury [3]. Similarly, patients with gain-of-function mutations in complement fraction C3 or complement factor B (CFB), which

controls C3 convertase stabilization, may lead to chronic uncontrolled complement activation against the endothelium in the genetic forms of aHUS.

The endothelial cells have anticoagulant properties, including synthesis of thrombomodulin, and maintenance of a low synthesis of tissue factor. Vascular endothelial disease or endothelial dysfunction by complement-mediated endothelial injury may result in decreased thrombomodulin synthesis, enhanced induction of tissue factor, and increased production of vWF, which synergistically promote intravascular thrombosis. Organ dysfunction as a result of aHUS is triggered by the formation of platelet aggregates on the endothelium and dissemination of microthrombi obstructing arterioles and capillaries and creating shear trauma to the erythrocytes as they traverse through the microcirculation, resulting in fragments that are observed as schistocytes on light microscopy.

A specific plasma metalloprotease ADAMTS13, also known as von Willebrand factor-cleaving protease, is a zinc-containing metalloprotease, secreted from hepatocytes and is the responsible enzyme for the cleavage of von Willebrand factor multimers. TTP is associated with severe deficiency of ADAMTS13 activity (<5%), however a mild reduction of ADAMTS13 function may be seen in patients with aHUS, which was verified in our patient. Variations of the ADAMTS13 gene (polymorphism) are partly responsible of the reduced ADAMTS13 function in aHUS [5].

Plasma exchange or plasma infusion has been used for treatment of aHUS. However, 65% of patients with aHUS require dialysis, have permanent kidney damage, or die within 1 year of diagnosis, likely secondary to a persistent underlying complement dysregulation and thrombotic microangiopathy [3,6]. Eculizumab is a monoclonal antibody that blocks the cleavage of C5, preventing the release of C5a, a potent anaphylatoxin and C5b, the initial protein of the cytotoxic membrane attack complex. Eculizumab is designed to suppress terminal complement activation. Clinical trials support the use of eculizumab for complement-mediated thrombotic microangiopathy and it is associated with substantial kidney recovery and improved clinical outcomes [6].

In conclusion, aHUS is a life threatening complication and can occur very early in post heart transplantation period, even in the absence of calcineurin inhibitor therapy. Given the dynamic changes in laboratory parameters after heart transplantation, a high index of suspicion and prompt life saving intervention is paramount in management of this potentially lethal syndrome.

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GRAPH 1. Laboratory data during hospitalization.

Plasma exchange therapy started on POD 3. Tacrolimus started on POD 8.



LDH (u/l)

Platelet  
(x1000/cu mm)

Haptoglobin  
(mg/dl)

Creatinine  
(mg/dl)

